UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/957,045	10/24/97	DALUGE S	PB1517US3

023347 HM12/1201
DAVID J LEVY, VP INTELLECTUAL PROPERTY
GLAXO WELLCOME INC
GLOBAL INTELLECTUAL PROPERTY
FIVE MOORE DR, PO BOX 13398
RESEARCH TRIANGLE PARK NC 27709-3398

EXAMINER	
BERCH, M	
ART UNIT	**PAPER NUMBER**
1624	20

DATE MAILED: 12/01/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/957,045	Applicant(s) Daluge
	Examiner Mark L. Berch	Group Art Unit 1624

☒ Responsive to communication(s) filed on *Oct 17, 2000* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *9 and 18-22* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *9 and 18-22* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

The request filed on 10/14/2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/957045 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 18-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The term "Glycosidic bond" is indefinite. There is no such thing as a "Glycosidic bond". There are a single, double, triple, dative, and normalized bonds, etc. For example, while the bond goes from the N-9 of the purine, the examiner does not even know whether the Glycosidic bond goes to a N, O or C. In the paper of 3/17/2000, applicants gave "an example of a Glycosidic bond". However, this explanation of what constitutes a "glycosidic bond" only makes matters worse. The arrow that applicants have labeled as being to a "glycosidic bond" in fact points to an ordinary single bond. Moreover, its application to the current claims is quite unclear. The claims are drawn

to preparation of purine derivatives, but there is no purine in this structure. Further, the bond depicted is not the bond which attaches the R^3 as required by the claim language, but rather appears to be a bond internally present within the R^3 moiety. Moreover, the remarks do not appear to be aware of this, referring to R^3 choices which are bound by N, i.e. which are substituted amines. See first full sentence on page 5 of the remarks. But that is impossible. R^3 cannot be bound by a N, unless that N is part of a heterocyclic ring as set forth in the last R^3 choice. Thus, for example, the moiety depicted on page 5, if bound by the N is not a permitted choice for R^3. Note previous discussion of this point in the Final Rejection over EP 413,544 in view of Norbeck, Vince, Borthwick or Shealy.

Beyond that, assuming that what the claim is trying to say is that R^3 cannot be a moiety derived from a sugar, the claim would still be indefinite. There is no single generally accepted definition of what does and does not constitute a sugar and hence what moiety would qualify as an aglycone piece. The material depicted at the bottom of page 4 has three OH groups. Would it still be an aglycone if one, two or three OH groups were missing, or if an additional OH or hydroxymethyl group were present, or if the two OH groups attached to the ring were attached to the same carbon instead of adjacent carbons? If the ring size were 4, 6, 7 or 10 instead of 5? If the ring had 1 sulfur, nitrogen or carbon instead of one oxygen, or if it had 2 oxygens instead of just one? If the ring were unsaturated, bridged or fused to another ring? If the ring had

other substituents such as amino, halo, acetoxy or a heterocycle? Are acyclic versions included in the definition of the aglycone?

2. The phrase, "an acyclic group, wherein the carbon atoms may be substituted by one or more heteroatoms" is redundant, and thus it is unclear what the intent is for all the material in the two substituents lists. An acyclic group by its very nature could already have heteroatoms; acyclic only requires that there be no rings present. Thus, e.g. C(O)H is an acyclic group. The same is true of all the substituents listed e.g. halogen. "Acyclic group" already provides for Halogen substituents.

3. Phosphonyl is indefinite. It means the radical derived from the removal of OH from a phosphonic acid, but which one? The paper of 8/2/99 is noted, which states that $-P(O)(OH)_2$ is intended. If that is what is intended then a) applicants must put that language into the claims, and b) applicants must show that one of ordinary skill in the art reading this specification would understand that this is what was intended, especially in view of the fact that this is actually called the "phosphoryl" group. Ordinarily, the term "phosphonyl" refers to something of the type RP(O)(OH), which leaves open the question of what R is.

4."Heterocyclic" is indefinite. What is the number and nature of the heteroatoms?. Page 10 does not state what the number or nature of the heteroatoms are. At least one must be N, S, or O, but could a second be replaced with Se or P? How many could there be?

5. The term "group" remains ambiguous. The question here is whether the "group" (to which optional substituent may be attached) must be entirely what the preceding adjective (carbocyclic or acyclic, respectively) requires, or just partially. Thus, a group like benzyl has an acyclic component (the CH_2) and a cyclic component (the benzene ring). But it is not entirely acyclic or carbocyclic. The term "group" is not clear as to whether such a mixed group is included. Is 4-(1-piperidinyl) phenyl permitted? Piperidinyl is not permitted as a substituent on the carbocyclic, so the question is, does a phenyl which is substituted by a heterocycle qualify as a heterocyclic group? Does "heterocyclic group" require that it be entirely (optionally substituted) heterocycle? The paper of 3/17/2000 states that "an ordinary dictionary definition" is intended, but this term is being used in a technical way. If applicants have a specific definition which sheds light on the above questions, they are invited to present it.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9, 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daluge '697 in view of Vince '224 or Daluge '671, further in view of Norbeck, Vince '607, Bothwick or Shealy.

The primary reference discloses applicants process in Column 8, lines 18-37, conversion of V to II, with one difference. Note that Z can be Cl (Column 7 line 64) and R^2 can be formyl (Column 7, line 29). The sole difference is that while prior art applicants do the reaction with the amine protected (with R^3), the claimed process is done with the amine not protected. This variation is shown in Vince '224 and Daluge '671. See Vince '224 example 22, which corresponds in the last step in scheme 1, use of 6b. In Daluge '671, See Example 4, where again the amine in the 2 position of the pyrimidine is unprotected.

The other difference is that the claims now require the use of aqueous acid for the orthoformate condensation. The Norbeck, Vince '607, Bothwick and Shealy references all show this directly. In Norbeck, see Column 11, 13-14. This is exemplified at Column 19, step G, which uses aqueous Hydrochloric acid, just as applicants do. In Vince see Figure 1, cyclization of 3a. Ex 11 uses the same procedure. In Bothwick, see paragraph bridging columns 17-18, using the same procedure. In Shealy, see Example 1, which uses the same acid. These references thus show that the use of aqueous acid is conventional for orthoformate cyclizations.

Applicants in the paper of 8/2/1999 made a lot of assertions without presenting evidence. For example, the Shealy process, which is there simply to show that it is known to use aqueous acid, has "contaminant which render this process unsuitable for large scale manufacture and formulation." But there is no evidence for this assertion. More specifically, the crucial issue is that of removing the N-2 protecting

group early (as is done by applicant) verses later as is done by Daluge. But this argument requires a showing that removal at the earlier stage unexpectedly gave fewer problems on deprotection than removal at a later stage. Instead, applicants merely assert (paragraph bridging pages 6-7 of the remarks) that this is so, without actually showing it. Whatever loses which occur when the N-2 protecting group is removed in the later stage as is done by Daluge must be balanced against the losses that occur when applicants remove their protecting group at the earlier stage. Applicants must actually show that this problem exists, not merely assume it.

In the paper of 3/17/2000, Applicants pointed to the low yield of Shealy, example 1, and problems with the Vince and Borthwick, etc. But these are not the primary references. These are solely a secondary references, cited only to show that the use of aqueous acid is conventional for orthoformate cyclizations (Norbeck, Vince '607, Borthwick or Shealy) or to show removing the N-2 protecting group early (as is done by applicant) rather than later. Thus, while the remarks state, "disadvantages of the '607 process are...", the claims are not rejected over the '607 process itself.

With regard to the essential difference, that is, removing the protecting group early versus late, applicants must actually demonstrate a difference, rather than make unsubstantiated assertions like, "deprotection before ring closure causes the compound to fall apart." The essential difference is that applicants remove the protecting group earlier rather than later. A direct side by side comparison must be made to show that unexpected effects arise from this, because the variation of

removing the protecting group later is shown by both Vince '224 and Daluge '671. It is not considered hindsight because that procedure was already shown in those two references (note that they are from different research groups). Especially, example 4 of '671 provides excellent motivation of a cyclization being successfully done with the 2-position being unprotected.

Claim 9, 18-20 is rejected under 35 U.S.C. 103(a) as being unpatentable over EP 413,544 in view of Norbeck, Vince, Bothwick or Shealy.

See page 3 of the primary reference, which describes the conversion of II to IA. R_x can be H (see e.g. page 5, line 30 and also page 14, line 8), and R_1' is Cl (see page 4, line 56). Indeed, this exact pair of choices is set forth at page 5, line 50. Q is set forth as formyl amino at page 3, line 46. Given the specific guidepost at page 5 to those two variables, and the fact that only two choices are given for Q, one of which is formylamino, it clearly falls within the page 3 disclosure. The use of orthoformate is disclosed at page 4, line 43.

The reference is silent on the use of aqueous acid; the secondary references, as indicated in the above rejection, show that this is conventional for orthoformate cyclizations. Applicants argued that the process "exclude amines where R^3 is OR or OH." This is simply not so. Indeed, OH and protected OH are recited in Claim 9 and page 10 calls them "preferred groups". The group in the reference, that is, $O(CH_2)_3OR_5$ is a protected OH. Thus, (II) of the primary reference falls within the VI of the claims. The examiner simply does not understand why it does not. Applicants in the paper of

8/2/1999 said, "R^3 cannot be unstable amines as described above." What does this mean? R^3 is not an amine, it is a substituent which is attached to an amino group. Note the lower right of VI. Thus, the question is, does the definition of R^3 in the claims embrace the $O(CH_2)_3OR_5$ of the prior art. Why doesn't it? To begin with, R^3 can be an "acyclic group". The $O(CH_2)_3OR_5$ is an acyclic group. Next applicants point out that the reference does not use aqueous acid. That is why there are secondary references. The reference is not asserted to be an anticipation, only that it renders the claims obvious.

With regard to better yields, etc, applicants must present a side by side comparison using the same substituent. Applicants in the paper of 3/17/2000 pointed to example 8 of their application, but that does not use the same substituent as is seen in the prior art. Applicants pointed out that the reference does not use aqueous acid but that is explicitly taught by the secondary references. The reference is not asserted to be an anticipation, only that it renders the claims obvious. Applicants present no justification for calling this a matter of hindsight. Four references show that the use of aqueous acid is conventional for orthoformate cyclizations. One of ordinary skill in the art of organic synthesis would thus be aware of such an expedient, and the fine results obtained in the secondary references would motivate their use.

Claims 9, 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Norbeck, Vince, Bothwick or Shealy, in view of EP 413,544 or Daluge '697.

The primary references are discussed above. These differ only in that they use in the 5-position the unsubstituted amino, whereas applicants use the formyl amino. However, the secondary references teach that both are alternatively useable for this cyclization. Note that Q in EP 413,544 and NHR^2 in Daluge '697 are both defined as being either amino or formyl amino.

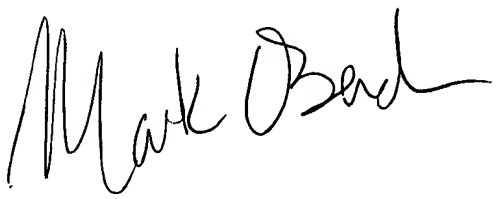
Largely the same issues arise here. The secondary references do not have to teach"benefits of making the claimed modification", only render it obvious. Both EP 413,544 and Daluge '697 do exactly that.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from

the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718.



Mark L. Berch

Primary Examiner

Group 1620 - Art Unit 1624

November 30, 2000